Negative Symptoms in Schizophrenia: A Comprehensive Review of Electrophysiological Investigations

Nash N. Boutros [1], Armida Mucci [2], Vaibhav Diwadkar [3], Rajiv Tandon [4]

Abstract

Clinical heterogeneity is a confound common to all of schizophrenia research. Deficit schizophrenia has been proposed as a homogeneous disease entity within the schizophrenia syndrome. Utilizing the Schedule for the Deficit Syndrome (SDS) has allowed the definition of a subgroup dominated by persistent clusters of negative symptoms. While a number of studies have appeared over the years examining the electrophysiological correlates of the cluster of negative symptoms in schizophrenia, only a few studies have actually focused on the deficit syndrome (DS). PubMed as well as MEDLINE were searched for all reports indexed for "negative symptoms" or "deficit syndrome" and one of the following electrophysiology assessment tools: electroencephalography (EEG), evoked potentials (EPs), or polysomnography (PSG). While this line of research is evidently in its infancy, two significant trends emerge. First, spectral EEG studies link increased slow wave activity during wakefulness to the prevalence of negative symptoms. Secondly, sleep studies point to an association between decrease in slow wave sleep and prevalence of negative symptoms. Several studies also indicate a relationship of negative symptoms with reduced alpha activity. A host of other abnormalities—including sensory gating and P300 attenuation—are less consistently reported. Two studies specifically addressed electrophysiology of the DS. Both studies provided evidence suggesting that the DS may be a separate disease entity and not simply a severe form of schizophrenia.

Key Words: Deficit Syndrome, Negative Symptoms, Schizophrenia, Evoked Potentials (EPs), Electroencephalography (EEG), Polysomnography (PSG)

Introduction

Functional or anatomical probing of individual psychiatric symptoms or symptom clusters within a psychiatric syndrome is a relatively recent endeavor. Schizophrenia symptomatology varies widely, affecting the cognitive, affective, and reality testing domains. Three sets of symptoms received particular attention: positive, negative and cognition-related symptoms. Based on the fundamental differences and likely brain structures involved in the generation of these symptom clusters, an assumption can be made that the underlying physiopathologies mediating these symptoms are different.

Electrophysiological research technology is non-invasive and relatively inexpensive. Research utilizing this methodology has pointed to a number of highly replicable physiological aberrations in individuals suffering from schizophrenia. None the less, no biological abnormality has proven to be diagnostic, or even present, in a significant majority of patients. One reason commonly advanced for such is the agreed upon heterogeneity of the syndrome. By

[1]Department of Psychiatry and Neurosciences, University of Missouri in Kansas City (UMKC), Kansas City, MO
[2]Department of Psychiatry, University of Naples SUN, Naples, Italy
[3]Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI
[4]Department of Psychiatry, University of Florida College of Medicine, Gainsville, FL

Address for correspondence: Nash N. Boutros, MD, Professor and Chairman, Department of Psychiatry and Neurosciences, University of Missouri in Kansas City (UMKC), 1000 East 24th Street, Kansas City, MO 64108
Phone: 816-512-7503; Fax: 816-512-7509;
E-mail: nboutros@med.wayne.edu

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Clinical Implications

While a number of studies have appeared over the years examining the electrophysiological correlates of the cluster of negative symptoms in schizophrenia, only a few studies have actually focused on the deficit syndrome (DS). And, while this line of research is evidently in its infancy, two significant trends emerge from this meta-analysis. First, spectral EEG studies link increased slow wave activity during wakefulness to the prevalence of negative symptoms. Secondly, sleep studies point to an association between decrease in slow wave sleep and prevalence of negative symptoms. Several studies also indicate a relationship of negative symptoms with reduced alpha activity. A host of other abnormalities—including sensory gating and P300 attenuation—are less consistently reported. Two studies specifically addressed electrophysiology of the DS. Both studies provided evidence suggesting that the DS may be a separate disease entity and not simply a severe form of schizophrenia.

identifying the aberrations that are more specifically linked to a particular symptom (e.g., hallucination) or to a symptom cluster (positive, negative or cognitive) advances can be made toward a better understanding of the different symptom clusters, as well as the disorder as a whole.

Negative symptoms of schizophrenia have been recognized for a long time as the most devastating among all symptoms clusters of schizophrenia. Research over the last few decades has demonstrated different biological and clinical correlates for phasic and enduring negative symptoms (1, 2). Enduring negative symptoms correlate with decreased functional outcome (3-10) and are refractory to common pharmacological interventions (3, 11-13). The development of the Schedule for the Deficit Syndrome (SDS) has allowed the definition of a subgroup of schizophrenia patients dominated by clusters of enduring negative symptoms (14). This subgroup of patients (deficit schizophrenia; DS) arguably suffers from the most severe and costly form of schizophrenia (13, 15).

Physiological probing of brain function and dysfunction uses two fundamentally different technologies: functional (as contrasted to structural) neuroimaging and electrophysiology. While neuroimaging has superior spatial resolution, electrophysiology enjoys a superior temporal resolution. It is widely agreed upon that the two methodologies are complementary (16), and efforts are underway for the simultaneous recording of both kinds of brain activity. In this review, we focus on electrophysiological investigations probing negative symptoms or the deficit syndrome, and attempt to leverage the existing electrophysiology literature in schizophrenia in an attempt to investigate the possibility of a unifying hypothesis for the pathophysiology of negative-symptom dominated schizophrenia patients.

EEG abnormalities in schizophrenia have been noted since the early days of electroencephalography. The emergence of the ability to analyze EEG signals with the aid of the computer allowed the intense and detailed interrogation of the complex bases of these rich electrophysiological data (17). Defining the electrophysiological changes most closely linked to negative symptoms may allow guided research to probe specific negative symptoms like apathy, amotivation and emotional blunting.

Methods

PubMed as well as MEDLINE were searched for all reports indexed for "negative symptoms" or "deficit syndrome" and one of the following electrophysiology assessment tools: electroencephalography (EEG), evoked potentials (EPs), event-related potentials (ERPs), or polysomnography (PSG). A number of papers were flagged by the searches as the articles included the terms "negative" or "negative symptoms," but upon further examination these papers did not include data relating negative symptoms to the electrophysiology modality examined. Such papers were excluded from the analysis (e.g., Force et al., [18]). Papers were then grouped together based on the specific electrophysiological modality examined. Data regarding the sample sizes, clinical assessments tools utilized, the specific electrophysiology technique used (e.g., in EP studies, which EP component was examined), and finally the results reported were collected.

Results

EEG Changes in Association with Negative Symptoms

Table 1 lists eleven studies that directly addressed the correlation between negative symptoms and EEG changes.

Table 1 highlights the varying EEG methodologies used in probing negative symptoms (and schizophrenia in general) (17). Despite the varying methodologies (standard vs. computer-aided analysis, examining coherence vs. examining spectral distribution), five of the eleven included studies that point to an increased slower activity (mainly theta rhythms of 4–8 Hz activity) in association with negative symptoms. A less frequently reported abnormality is related to reactivity and predominance of faster rhythms (beta activity). A relatively recent study supported the observation of a significant correlation between increased theta activity

Table 1 Electroencephalography

Study, Year (Ref #)	Sample	Assessment	Measurement	Findings
Williamson et al., 1989† (64)	20 Sch, 20 HC	DSM-IIIR SCID	Spectral EEG resting and during WCST	Negative symptoms correlate with smaller increase in beta during WCST.
Kessler et al., 1991 (65)	18 Sch (med free), 13 HC	DSM-IIIR Diagnostic Interview Schedule	Spectral EEG with auditory emotionally salient and control stimuli	Residual/Undifferentiated subgroup with predominant negative symptoms showed more beta1 and less alpha at temporal sites and more beta1 and beta2 at frontal sites vs. controls; they had different lateralization patterns in the delta band after emotionally salient stimuli.
Merrin & Floyd, 1996* (66)	17 Sch (med free 14 days)	DSM-IIIR by the SADS, BPRS	Spectral EEG	Reduced alpha power, decreased alpha coherence between hemispheres associated with negative symptoms.
Sponheim et al., 1997 (67)	28 Sch winter born, 81 Sch (non- winter born), 18 Non-Sch psychosis	PSE, DSM-III	Non-winter born Sch and non-schizophrenia	This paper strongly documents heterogeneity within schizophrenia groups. Psychotic patients had increased low frequency and decreased alpha power. Winter-born Sch and non-schizophrenia psychotic patients had no power abnormalities.
Sponheim et al., 2000* (68)	112 Sch, 78 Psychotic Non-Sch, 107 Controls	PSE, DSM-IV	EEG spectral, relative, only clozapine data examined	Low alpha-high slow activity factor scores associated with negative symptoms in Sch patients.
Knott et al., 2000† (69)	17 Sch free of neuroleptics	DSM-IIIR, Clinical, PANSS	EEG spectral analysis, intra- and inter-hemispheric coherence	No clear correlate of negative symptoms pre-clozapine treatment. Greater inter-hemispheric theta and beta asymmetry predicted good response in both positive and negative symptoms. Greater intra-hemispheric delta asymmetry also predicted response of negative symptoms.
Winterer et al., 2000 (70)	Two trainer (33 Sch, 49 Con) and a test set (32 Sch, 49 HC)	ICD-10 Clinical Interview	EEG spectral resting and activated and auditory-evoked responses	Patients with predominantly negative symptoms were more readily classifiable based on frontally pronounced delta activity and decreased power of the N100/P200 evoked response.
Strelets et al., 2002* (71)	Only male subjects. 16 Positive Symptoms Sch, 20 Negative Symptoms Sch, 16 HC	DSM-IIIR Clinical Interview	High frequency oscillation connectivity	Decreased connectivity between frontal regions in negative symptoms patients.
Fehr et al., 2003† (72)	30 Sch (9 unmedicated), 17 HC	DSM-IV Clinical Interview, PANSS	MEG,spectral analysis	Relative % of slow activity in temporal regions correlated with negative symptoms.
Manchandra et al., 2008† (73)	117 first-episode psychosis	SCID-IV, SAPS, SANS	Standard (visually inspected) EEG (sEEG)	Pre-treatment sEEG abnormalities predict poorer response of both positive and negative symptoms.
Venables et al., 2009† (19)	48 Sch (medicated), 61 1st-degree relatives	25-item BPRS	Spectral analysis	Increased theta activity during eyes closed condition in Sch.

Applicability to the deficit syndrome: *likely applicable, description clear; †possibly applicable; ‡description inadequate for a determination. Sch=schizophrenia; HC=healthy controls; PSE=Present State Exam; sEEG=Standard visually-inspected EEG; BPRS=Brief Psychiatric Rating Scale; SADS=Schedule for Affective Disorders and Schizophrenia; SANS=Scale for Negative Symptoms; SAPS=Scale for Positive Symptoms; SCID=Standardized Clinical Interview for DSM; PANSS=Positive and Negative Syndrome Scale; MEG=megnetoencephalography; WCST=Wisconsin Card Sorting Test.

and negative symptoms (19). In this study, the strongest correlations were obtained from frontal, central and occipital regions while correlation between EEG data obtained from temporal regions and negative symptoms barely reached significance. This observation suggests that the increased theta seen in association with negative symptoms may be more represented in certain brain regions and may have significant implications to the eventual identification of the specific circuitry underlying the development of these symptoms (19). To our knowledge, no study has specifically investigated the spectral EEG profile of patients with DS or differentiated between enduring and phasic negative symptoms.

EP Changes Associated with Negative Symptoms

Table 2 lists seventeen studies that directly examined the correlation between negative symptoms and evoked potential (EP) changes.

Mid-Latency Auditory Evoked Responses and Sensory Gating

The mid-latency auditory evoked responses (MLAERs) have been extensively used to study information processing both in mental health and disease. Numerous studies have shown two particular components to be abnormally reduced in amplitude in patients with schizophrenia. These two components are the N100 (a negative component seen approximately 100 msec following an auditory stimulus) and the P50 (a positive component seen about 50 msec after the presentation of an auditory stimulus) (20). The N100 component has been extensively examined in schizophrenia patients. The majority of studies report decreased amplitude of the N100, which is not readily attributable to medication effects (21). The P50 MLAER has also been used extensively to examine the phenomenon of amplitude attenuation with stimulus repetition. The term "sensory gating" has been linked with studies of sensory inhibition utilizing the P50 MLAER in a paired click paradigm, commonly used to study "sensory gating." In a paired click paradigm, two identical stimuli (S1 and S2) are delivered with a short inter-stimulus interval of 500 msec and a longer inter-pair interval of 8–10 sec (22). A sensory gating deficit has been repeatedly demonstrated in schizophrenia patients (22-25). Meta-analysis of the P50 gating deficit in groups of non-selective schizophrenia patients found the effect size to be more modest than earlier reports suggested (26). Heterogeneity of both methodology and composition of patient groups were suggested as possible causes for variation in results. Abnormal sensory gating has been proposed as a fundamental mechanism by which psychotic symptoms evolve (24). Data from our laboratory suggest that the gating deficit—particularly of the N100 component—is mainly found in association with the negative symptoms of schizophrenia (25). N100 amplitude is commonly (but not invariably) found to be reduced in patients with schizophrenia (21) and in unaffected first-degree relatives of the same patients (27). The relationship between N100 amplitude and symptoms remains unclear (21).

The gating deficit as assessed by the P50 component was examined in relationship to negative symptoms and was not found to correlate with any symptom cluster in earlier studies (28, 29). Subsequent investigations of gating of the P50 MLAER component reported a significant correlation with negative symptoms (30-32). Most recently, Santos et al. (33) investigated P50 gating in patients with DS and in those with non-deficit schizophrenia (NDS). These authors did not find differences in P50 gating between the two groups of patients, but found an association between the abnormality of P50 gating and poor functional outcome. These contradictory findings suggest that the relationship between primary, enduring negative symptoms and the P50 gating deficit is not simple or straightforward and may depend strongly on the specific composition of the study sample. It is also possible that the effect size of the observation is not robust enough to be detected in smaller samples or in the presence of a high noise to signal ratio as is common in P50 studies due to the relative small amplitude of the component (25). Furthermore, the specific scale or instrument used to assess the negative symptoms (or for that matter any symptom cluster) may also influence the correlations identified (25). An alternative hypothesis is that a mediating variable (not as yet identified), cross-correlated with negative symptoms and gating deficits (e.g., poor outcome), is responsible for the association between P50 gating deficit and negative symptoms. Further studies are needed to clarify the issue.

ERP Aberrations Associated with Negative Symptoms of Schizophrenia

Event-related potentials (ERPs) are a special subset of EPs that are of great interest to psychophysiologists as they are only generated when the brain performs a psychological or cognitive function (e.g., attention, memory upgrade, deviance detection). Thus, these ERPs are very sensitive to many psychological variables like level of arousal and motivation. This is in contrast to the more obligatory EPs (like the P50, N100 or P200) that are produced simply by sensory stimulation. The most extensively studied ERP components include the P300 (34) as well as the mismatch negativity (MMN) (35), which were found to be abnormally small (and sometimes delayed) in schizophrenia populations. For the MMN component, no correlation with negative symptoms has been reported (35). No study specifically examined MMN in groups of DS patients.

Table 2 Evoked Potentials

Study, Year (Ref #)	Sample	Assessment	Measurement	Findings
Pfefferbaum et al., 1989 (40)	31 Sch, 37 HC	BPRS	P300 amplitude	P300 smaller in patients with a positive correlation with negative symptoms in unmedicated patients.
Adler et al., 1990† (28)	20 medicated (9 predominantly negative) Sch, 12 Control		P50 gating	No correlation of P50 gating and negative symptoms.
Boutros et al., 1991† (23)	13 medicated non-paranoid and 13 paranoid Sch, and 13 Control	BPRS	P50 amplitude and gating	P50 amp and gating decreased in non-paranoid patients.
Boutros et al., 1993† (74)	13 paranoid Sch, 11 non-paranoid (all unmedicated), 11 HC	DSM-IIIR Clinical Interview	P50 amplitude	P50 amp decreased in non-paranoid patients.
Turetsky et al., 1998* (50)	65 Sch (30 unmedicated), 48 HC	BPRS, SANS, SAPS	P300	Asymmetrical P300 reduction only in NDS while DS patients had reduction in r-parietal.
Baldeweg et al., 2001 (75)	14 medicated Sch, 14 Control	ICD-10 (Clinical Interview, Manchester Scale, digit span, verbal fluency)	Duration MMN	No correlations with symptoms clusters.
Jeon & Polich., 2003 (52)	Literature review	NA	P300	No overall correlation with negative symptoms but a strong negative correlation with paranoid symptoms.
Boutros et al., 2004 (29)	23 medicated Sch (atypical neuroleptics), 23 Control	PANSS	P50 gating	No relationship between P50 gating and negative symptoms.
Ringel et al., 2004 (30)	34 Sch (medicated), 12 HC	PANSS	P50 gating	P50 gating correlation + with negative symptoms.
Louchart-de la Chapelle et al., 2005 (31)	81 Sch (medicated), 88 HC	SAPS & SANS	P50 gating and P50 latency	P50 gating decrease in general but more in association with negative symptoms.
Thoma et al., 2005* (76)	20 Sch (medicated)	SCID for DSM-IV, SANS, PANSS	P50 EP and MEG gating	No relationship between P50 (EP) gating and negative symptoms. Right hemisphere M50 (MEG) gating ratios positively correlated with negative symptoms (worse gating-more negative symptoms).
Arnfred, 2006* (32)	17 Sch spectrum (unmedicated), 24 HC	SANS & SAPS	P50 EP and P50 gating	Difference wave calculated by subtracting S2 wave from S1 wave. Decreased P50 amplitude and difference wave in patients with severe negative symptoms.
Toyomaki et al., 2007‡ (77)	23 Sch (medicated)	SCID & Wisconsin Card Sorting Test	Duration MMN	Strong correlation between MMN amplitude and executive functioning.
Mucci et al., 2007* (51)	40 medicated Sch (DS=20; Non-DS=20), 20 HC	SANS/SAPS & EBPRS	N100 and P300	Double dissociation: N100 small in DS and P300 small in non-DS.
Boutros et al., 2009† (25)	45 medicated Sch, 49 HC	PANSS	P50, N100, P200 gating	N100 gating deficit correlates with negative symptoms.
Santos et al., 2010* (33)	60 DS, 60 non-DS, 60 HC	SDS	P50 gating	No correlation to negative or positive symptoms, but patients in general had worse gating which correlated with poor outcome.
Olincy et al., 2010 (78)	181 medicated Sch, 333 HC	SCID & SANS/PANSS	P50 gating	P50 gating decreased in group in general, but no correlation with clinical clusters.

Applicability to the deficit syndrome: *likely applicable, description clear; †possibly applicable; ‡description inadequate for a determination.
Sch=schizophrenia; HC=healthy controls; SDS=Schedule for the Deficit Syndrome; BPRS=Brief Psychiatric Rating Scale; SANS=Scale for Negative Symptoms; SAPS=Scale for Positive Symptoms; SCID=Standardized Clinical Interview for DSM; PANSS=Positive and Negative Syndrome Scale; EP=evoked potential; MMN= mismatch negativity; MEG=megnetoencephalography; DS=deficit schizophrenia; NDS=non-deficit schizophrenia.

As to P300, an amplitude reduction is considered a potential neurobiological vulnerability marker of schizophrenia (36). This amplitude reduction in auditory modality is a robust finding, unaffected by chronicity or medication status (36). The P300 amplitude reduction, in the auditory modality, is also observed in unaffected relatives (37, 38). Recent studies have shown that individuals at high risk for psychosis also show reduced auditory P300 amplitude (39), providing further support for auditory P300 reduction as a vulnerability marker. Some studies reported reduced amplitude also for the visual P300, but findings regarding this abnormality have been inconsistent (40).

Both studies provided data suggestive that the deficit syndrome is not simply a severe form of schizophrenia but more likely a separate clinical entity.

P300 amplitude reduction was found in association with negative symptoms by some (40-42) but not all studies (43-49). Only two papers specifically addressed ERPs in the deficit syndrome (50, 51). Both studies provided data suggestive that the deficit syndrome is not simply a severe form of schizophrenia but more likely a separate clinical entity. Turetsky et al. (50)—while not employing the Schedule for the Deficit Syndrome (SDS)—used the Brief Psychiatric Rating Scale, the Scale for Negative Symptoms, and the Scale for Positive Symptoms to address the criteria for the deficit syndrome. They examined the P300 component and found two patterns that cannot be seen as different grades of the same process. Patients with NDS showed the greatest reduction over the left temporal region while the DS subgroup showed the greatest reduction over the right parietal region. The second study specifically addressed the DS—using the SDS to characterize the syndrome—and found a double dissociation where only NDS patients exhibited the asymmetrical left temporal P300 amplitude deficiency, while DS patients exhibited a decreased amplitude of the N100 (51). It is of interest that Jeon and Polich (52), in an extensive meta-analysis, found no correlation between P300 amplitude and negative symptoms.

Sleep Changes in Association with Negative Symptoms

Table 3 lists eight studies that directly reported on the association between sleep architectural changes and negative schizophrenia symptoms.

Decreased delta sleep in association with negative symptoms has been a relatively consistent finding in schizophrenia patients (2). Of the eight studies identified, seven reported decreased slow wave sleep (SWS) in association with negative symptoms. Of these seven papers, five found a significant negative correlation between the severity of negative symptoms and percent of SWS (i.e., with increased severity of negative symptoms, less SWS is noted).

Discussion

While there is a significant volume of research attempting to probe the biological correlates of schizophrenia negative symptoms (53), studies specifically addressing the deficit syndrome (i.e., specifically meeting recently established criteria for this syndrome) remain sparse.

Two prominent/reasonably consistent electrophysiological correlates of negative symptoms emerge through this review: increased slow frequencies during wakefulness (as assessed by awake spectral EEG) and decreased slow wave sleep during night time recording.

While the largest group of studies identified were those related to EP/ERP findings, a consistent or strong trend was difficult to identify, perhaps due to the tendency of different research groups to examine one particular EP component like P300, MMN, or sensory gating. Studies examining a number of EP components simultaneously are sparse. Despite the small number of studies and the varying EP components examined, the literature points to a deficit in the sensory gating of the mid-latency evoked responses reported from more than one laboratory (25, 30, 31). Furthermore, a decreased amplitude of the N100 response has also been linked to the deficit syndrome (51). It is of importance to note that a meta-analysis of the P300 ERP in schizophrenia found a correlation with positive but not negative symptoms (52). Mucci et al. (51) were able to corroborate this finding in a group of well-characterized DS patients.

As is mentioned above, different laboratories tend to focus on one aspect of one methodology; for example, examining the P300 ERP in an evoked potential laboratory or examining EEG coherence in an EEG laboratory. This, of course, is a direct reflection of the research expertise represented in the particular laboratory. On the other hand, this drawback represents a significant missed opportunity to collect much needed data from difficult to identify patient groups. We have recently advocated the need to develop more comprehensive electrophysiology laboratories, at least in academic departments of psychiatry, which should readily alleviate this shortcoming (16). It is a fact that almost all electrophysiology technologies (perhaps with the exception of magnetoencephalography, which is costly to purchase, install, maintain and operate) utilize similar technologies and require similar expertise for data analysis and reporting. Multi-level electrophysiological studies will help further

Table 3 Sleep

Study, Year (Ref #)	Sample	Assessment	Measurement	Findings
Ganguli et al., 1987† (79)	8 Sch (drug naive), 16 HC	BPRS, Wing Negative Symptoms Scale (80)	Standard sleep analysis	An inverse relationship between slow wave sleep and negative symptoms.
van Kammen et al., 1988† (80)	10 Sch (unmedicated)	SANS (82), Bunney-Hamburg Global Assessment Scale for Psychosis (83)	Standard sleep analysis	An inverse relationship between slow wave sleep and negative symptoms.
Neylan et al., 1992† (81)	18 Sch (haloperidol), repeat drug free (n=9)	Bunney-Hamburg Scale, SADS	Standard sleep analysis	An inverse relationship between slow wave sleep and negative symptoms.
Keshavan et al., 1995† (82)	24 Sch (5 delusional disorder), unmedicated	BPRS, SANS, SAPS, SCID	Standard and automated sleep analysis	An inverse relationship between slow wave sleep and negative symptoms.
Kato et al., 1999‡ (83)	7 Sch	DSM-IV Clinical	Standard sleep analysis	An inverse relationship between slow wave sleep and negative symptoms.
Tandon et al., 2000* (2)	60 Sch (drug free)	SADS and RDC	Standard sleep analysis	An inverse relationship between REM latency and SWS and negative symptoms.
Müller et al., 2004* (84)	10 Sch (drug free)	DSM-IV (Clinical), PANSS	Standard sleep analysis	Decreased SWS and REM percentage.
Poulin et al., 2008* (85)	10 Sch (first episode, drug naive), 30 Control	DSM-IV Clinical & BPRS	Spectral analysis	Magnitude of absolute alpha correlated positively with negative symptoms.

Applicability to the deficit syndrome: *likely applicable, description clear; †possibly applicable; ‡description inadequate for a determination. Sch=schizophrenia; HC=healthy controls; BPRS=Brief Psychiatric Rating Scale; SADS=Schedule for Affective Disorders and Schizophrenia; SANS=Scale for Negative Symptoms; SAPS=Scale for Positive Symptoms; SCID=Standardized Clinical Interview for DSM; PANSS=Positive and Negative Syndrome Scale; RDC=Research Diagnostic Criteria; SWS=slow wave sleep.

define the abnormalities detected. For example, if an EEG or EP abnormality disappears during sleep, this would influence the understanding of its pathophysiology as compared to the abnormality being persistent during sleep. If an EP abnormality is linked to a particular EEG state, this finding would be of significance for the eventual defining of the neural circuitry mediating this abnormality.

The current level of knowledge is inadequate to propose a unifying theory of the pathophysiology underlying the described anomalies. However, most studies suggest pervasive bottom-up deficiencies that may lead to cascading information processing problems. This tentative conclusion is based on the observation that information processing abnormalities gleaned from EP studies (the only investigative methodology that can assess chronology at a millisecond-by-millisecond level in the intact behaving human) tend to occur earlier in the sequence of EPs and start during periods that are commonly considered as "pre-attentive." Sleep deviations suggest a serious abnormality of the restorative deep sleep stages and the awake EEG abnormality suggests difficulty generating the faster frequencies, reflecting decreased ability to generate efficient smaller neuronal ensembles to deal with more focused or effective information processing. A unifying hypothesis of the deviant oscillations during wakefulness (increased slow activity) and during sleep (decreased SWS) could point to a dysfunction involving thalamocortical circuitry (54, 55). Thalamocortical circuits exhibit two fundamentally different modes of operation across the sleep-wake cycle: a state of tonic activation (desynchrony) during waking and REM sleep, and a state of rhythmic synchronized activity during SWS (56). Thalamic relay receives significant input from a number of brain stem structures and, thus, are subject to changes with a number of ascending neurotransmitter inputs. Furthermore, thalamic relay neurons also send collateral projections to the thalamic reticular nucleus, which are reciprocally inhibitory (GABAergic) with thalamic nuclei (57). The thalamus (and, more specifically, the reticular nucleus) has been proposed to be important for the function of sensory gating, which has been repeatedly shown to be deficient in schizophrenia (58) and may be more specifically associated with negative symptoms (58). Kirkpatrick and Buchanan (59) proposed

a neural circuit that may be at the heart of the DS. Components of this circuit include the amygdala, periamygdalar cortex, and parts of the prefrontal cortex. A number of thalamic nuclei (including the anterior, midline, mediodorsal, lateral anterior, and lateral dorsal as well as the intralaminar) have extensive connections with all these components and have been considered parts of the "limbic thalamus" (60). The involvement of the thalamus is also supported by observation of worsening of somatosensory gating in patients with thalamic strokes with recovery of the function over time (61). Consistent with this picture is the fact that EP abnormalities mostly suggest early information processing problems. In fact, recent reviews suggest a central role for thalamic abnormalities in the generation of schizophrenia symptomatology (62).

In order to move the field forward, we feel that it is of importance to first establish findings strongly and reliably associated with the deficit syndrome or with individual negative symptoms. It is at this stage that the specific correlates of a finding can be defined.

Based on the above, it can be stated that while research on the electrophysiological correlates of the deficit syndrome and enduring negative symptoms remains minimal, available data strongly support the need and likely profitability of this line of investigation. Most notably is the absence of studies where EPs, EEGs and sleep studies are performed in the same individuals in order to examine the correlation and interrelationships among these deviations.

In conclusion, it is clear that the field remains far from identifying any solid correlates of any of the symptoms, symptom clusters or the syndromes as a whole. In order to move the field forward, we feel that it is of importance to first establish findings strongly and reliably associated with DS or with individual negative symptoms. It is at this stage that the specific correlates of a finding can be defined.

Electrophysiology has the distinct advantages of being inexpensive and completely non-invasive. It is rather easy to add on electrophysiological investigations to ongoing studies without having any influence on the mother study. As a next essential step, examining the correlations among the related physiological aspects (EEG, EP/ERP/sleep) for better delineation of the specificity of findings (e.g., does the abnormality link to EPs but not underlying ongoing EEG? is the effect only during wakefulness or extends into sleep?). These two steps are essential before prospectively designed multimodality studies are proposed which tend to be very expensive. In fact, the likelihood of negative or false, possibly misleading, findings is high when correlating less than well-established observations. We would also like to note that—at this stage of the development of functional imaging investigations of negative symptoms or the deficit syndrome—we contend that the situation is not much better than in the electrophysiology field. Meta-analyses suggest that rather than specific focal deficits, DS subjects show general deficits in global cognition, without a clear selective deficit (63). This concept would benefit from a more informed input from electrophysiology investigations where highly accurate temporal deviations in neural connectivity can be elucidated. A separate review focused on functional imaging findings is currently being developed.

We further propose that once reasonably well-established electrophysiology correlates of negative symptoms are identified, investigators should begin to find commonality with other probing measures like imaging and genetics. Finally, based on accepted knowledge, investigators can begin to develop proposed circuitries that may underlie the disorder, and use the proposed circuitries to further define the physiological and structural deviation correlates of the disorder or specific symptoms.

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